SECTION II
REMARKS

Rejection of Claim 22 Under 35 USC § 112

Claim 22 was rejected under 35 USC § 112, second paragraph, as indefinite by recitation of the term "a more intense lysis." Applicants respectfully submit that this term is clear and that the claim defines the phrase. The complete phrase as recited in claim 22 is "inducing a more intense lysis of CD30 carrying cells *in vitro* than bimAbHRS-3/A9 (DSM ACC 2142)" (emphasis added).

MPEP §2173.05(b) ("Relative Terminology") states the apposite rule in the first heading of such section:

"WHEN A TERM OF DEGREE IS PRESENT, DETERMINE WHETHER A STANDARD IS DISCLOSED OR WHETHER ONE OF ORDINARY SKILL IN THE ART WOULD BE APPRISED OF THE SCOPE OF THE CLAIM"

and this rule of construction as applied to claim 22 shows such claim to be fully compliant with 35 USC §112, second paragraph. The standard for the terms in question is the lysis intensity of CD30 carrying cells *in vitro* by bimAbHRS-3/A9 (DSM ACC 2142), a standard against which the Fv antibody construct of claim 1 is compared, and from which one of ordinary skill in the art is fully apprised of the scope of claim 22.

In addition, Example 3(B) of the specification sets forth a method (see, for example, the 2nd paragraph on page 10 of the specification) by which a skilled person is easily able to compare the lytic activity of a F_v construct of the invention with that of the bimAbHRS-3/A9 antibody. Such comparison allows a determination of whether the F_v construct has a higher or lower lytic activity compared with that of the bimAbHRS-3/A9 antibody. Such determination is readily made and does not constitute an undue burden on one of ordinary skill in the art.

Claim 22 thus is clear and definite on its face. Accordingly, withdrawal of the rejection is respectfully requested.

Claim 22 has been further rejected under 35 USC § 112, first paragraph, as failing to comply with the enablement requirement of that section. Specifically it is contended in the Office Action that bimAbHRS-3/A9 may not be known and readily available to the public. Applicants respectfully disagree.

The antibody bimAbHRS-3/A9 (DSM ACC 2142) is the subject matter of US 5,643,759 (claim 1). Therefore, it is submitted that the USPTO already has acknowledged the fulfillment of the deposit requirements under §112 in connection with the bimAbHRS-3/A9 antibody, in particular that the deposited antibody is freely accessible. The antibody is freely accessible from the DSM depository as DSM ACC 2142.

Accordingly, withdrawal of the rejection is respectfully requested.

Additional Rejection Under 35 USC § 112

Claims 1-6, 15, 19 and 22 have been rejected under §112, first paragraph, as failing to comply with the written description requirement. The Office has contended that the phrase "inducing regression of Hodgkin's disease *in vivo*" is not supported by the original disclosure.

In fact, such terminology is supported in the specification at page 2, lines 5-6 ("can induce a regression of Hodgkin's disease"). Further clear support may be found in the specification at Fig. 4. Fig. 4 shows the treatment of SCID mice carrying Hodgkin's disease xenografts with an F_v antibody construct according to the invention. The results are discussed in Example 3(C) on pages 10 and 11 of the specification; see, e.g., lines 9-11 at page 11 ("an antibody construct according to the invention can activate NK cells both in vitro and in vivo, lysing $CD30^+$ L540CY Hodgkin's disease cells"). It is clearly discernable from Fig. 4 that the tumor volume regressed upon treatment with an antibody according to the invention (see also the description of Fig. 4 on page 6 of the specification, in respect of the graph of tumor volume as a function of days after treatment).

Accordingly, the phrase "inducing regression of Hodgkin's disease *in vivo*" is clearly and specifically supported by the original disclosure as filed and therefore does not add new matter. Withdrawal of the rejection is correspondingly merited and respectfully requested.

Rejections under 35 USC § 102(a)

The rejection of claims 1-6, 15, 19 and 22 under §102(a) as being anticipated by Arndt et al. has been maintained from the prior Office Action of March 13, 2006. It is respectfully submitted that Arndt et al. was published after the priority date of the present application and therefore does not qualify as "prior art" under 35 USC §102(a).

The pending claims are fully entitled to the foreign priority of DE 199 37 264. The Examiner's attention is respectfully directed to applicants' Express Mail submission to the USPTO on August 11, 2006 of an English translation of the priority document and certification of such translation. A copy of the return postcard received from that submission is attached hereto as Appendix A, evidencing the USPTO receipt of such certification and translation of the priority document. Accordingly, the present application is entitled to the priority date of DE 199 37 264 and Arndt et al. therefore does not qualify as prior art. Withdrawal of the rejection therefore is respectfully requested.

Additionally, claims 1-5 and 15 were rejected under 35 USC §102(b) as being anticipated by Hartmann et al. (Blood, 1997). In particular, it is stated in the August 24, 2006 Office Action that Hartmann et al. teach that side effects such as HAMAs in the anti-CD16/CD30 bispecific antibody treatment can be resolved by bispecific single-chain antibodies. Applicants respectfully disagree.

In Hartmann et al., the reference to single chain antibodies or diabodies is found in the paragraph bridging the left and the right column on page 2046. This paragraph relates to a general discussion of side effects connected with "a BiMoAb therapy" (emphasis added). The authors merely hypothesize that F_v constructs could overcome side effects connected with monoclonal antibody therapy. However, this discussion about the use of the genus of F_v constructs does not anticipate any species of F_v constructs having anti-CD16/CD30 specificities. The Hartmann et al. reference refers only to bispecific antibodies of the IgG type. The generic reference on page 2046 to single-chain antibodies for resolving problems associated with a monoclonal antibody therapy does not in any way contemplate the specifically claimed species of applicants'

invention. Further, Hartmann et al. do not disclose or suggest any F_v constructs that "induce regression of Hodgkin's disease *in vivo*."

Accordingly, Hartmann et al. fail to anticipate the subject matter of claims 1-5 and 15. Withdrawal of the §102(b) rejection is therefore appropriate and such action is respectfully requested.

Rejection Under 35 USC § 103

The rejection of claims 1-6, 15, 19 and 22 under 35 USC § 103(a) as obvious over Hartmann et al. (Leukemia and Lymphoma, 1998) in view of Holliger et al. has been maintained from the March 13, 2006 Office Action.

Applicants respectfully submit that in light of the cited references, it would not have been obvious at the time of the invention that a bispecific F_v construct would be capable of inducing a regression of Hodgkin's disease *in vivo*, as claimed.

Hartmann et al. specifically teach the use of anti-CD16/CD30 IgG antibodies for immunotherapy. Hartmann et al. do not teach or in any way suggest switching to any other antibody format for immunotherapy.

While Holliger et al. teach that antibody fragments may be preferable with regard to avoiding side effects caused by the F_c region of IgG antibodies and associated with the unwanted targeting to cells expressing F_c receptors, Holliger et al. do not teach or suggest that a bispecific F_v construct would have been capable of inducing a regression of Hodgkin's disease *in vivo*.

Holliger et al. merely teach that bispecific F_v diabodies bind to the respective antigen *in vitro*. However, Holliger et al. do not teach or indicate any cytotoxic or tumoricidal activity of the F_v constructs. Therefore, at the time of the invention, one of skill in the art could not have derived from Holliger et al. whether F_v constructs could exhibit a cytotoxic or tumoricidal activity *in vivo*. Holliger et al. do not contain any indication whatsoever about any cytotoxic *in vivo* activity. Thus, a skilled person considering the teaching of Holliger et al. would not have had a reasonable expectation of success (or, for that matter, any basis for any expectation of success) that a F_v construct could induce a regression of Hodgkin's disease *in vivo*.

Additionally, the diabodies (approx. 60kD) of Holliger et al. are smaller than and structurally different from the IgG antibodies (approx. 150kD) of Hartmann et al. At the time the invention was made it was not known in the art that a diabody according to the teaching of Holliger et al. had any capability of immune recruitment by targeting and activating natural killer cells *in vivo*. As Holliger et al. lack a teaching of a cytotoxic or tumoricidal activity of the F_v constructs, a skilled person would not have been motivated to switch from the IgG antibodies of Hartmann et al. to the diabodies of Holliger et al., because it could not have been extrapolated from the *in vitro* binding affinity data of Holliger et al. with any reasonable expectation of success that F_v constructs of anti-CD16/CD30 specificity are capable of inducing a regression of Hodgkin's disease *in vivo*.

Therefore, claims 1-6, 15, 19 and 22, reciting a F_v antibody construct having variable domains for CD16 and CD30 that induces a regression of Hodgkin's disease *in vivo*, find no derivative basis in Hartmann et al. in view of Holliger et al.

Withdrawal of this 35 USC § 103(a) rejection is therefore respectfully requested.

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ATTY DOCKET No. 4121-135

CONCLUSION

Based on the foregoing, all of Applicants' pending claims 1-6, 15, 19 and 22 are patentably distinguished over the art, and are in form and condition for allowance. The Examiner is requested to favorably consider the foregoing and to responsively issue a Notice of Allowance.

If any additional issues remain, the Examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same, in order that any residual issues can be promptly resolved, in favor of issue of a patent on the present application at an early date.

Respectfully submitted,

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Enclosures:
Appendix A [1 page]
Statement under 37 CFR 3.73 [1 page]

The USPTO is hereby authorized to charge any deficiency or credit any overpayment of fees properly payable for this document to Deposit Account No. 08-3284

ATTY DOCKET NO. 4121-135

APPENDIX A

This confirms receipt of:
Submission of Certified Copy of Priority German Patent Application No. 199 37 264.0, and its English Translation in U.S. Patent Application No. 10/049,404

In re U.S. Patent Appl. of:	ARNDT, Michaela, et al.
U.S. Patent Appl. No.	10/049,404
Date Filed:	February 5, 2002
Title:	FV ANTIBODY CONSTRUCT COMPRISING BINDING SITES FOR A CD16 RECEPTOR AND A CD30 SURFACE PROTEIN
Date Mailed:	August 11, 2006
Express Mail Label:	EO 010 427 915 US
Attorney Ref:	4121-135

(1) Submission of Certified Copy of Priority German Patent Appl. No. 199 37 264.0 [2 pgs.]
(2) Certified Copy of German Patent Application No. 199 37 264.0 [1 document]
(3) English Translation and Certificate of Verification of German Patent Application No. 199 37 264.0 [1 document]
(4) Return Postcard

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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Arndt, et al.

Application No./Patent No.: 10/049,404 Filed/Issued Date: February 5, 2002

Entitled: FV ANTIBODY CONSTRUCT COMPRISING BINDING SITES FOR A CD16 RECEPTOR AND A CD30 SURFACE PROTEIN

Deutsches Krebsforschungszentrum Stiftung des öffentlichen Rechts (Name of Assignee) an institute (Type of Assignee, e.g., corporation, partnership, university, etc.)

states that it is:

1. [X] the assignee of the entire right, title, and interest; or

2. [ ] an assignee of less than the entire right, title, and interest.
The extent (by percentage) of its ownership interest is _____%

in the patent application/patent identified above by virtue of either:

A. [X] An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel/Frame 013155/0367, or for which a copy thereof is attached.

OR

B. [ ] A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel/Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the United States Patent and Trademark Office at Reel/Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
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[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Signature	October 24, 2006 Date
Steven J. Hultquist Printed or Typed Name	(919) 419-9350 Telephone Number
Attorney for Applicants Title	

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.